

REMARKS/ARGUMENTS

In the Office Action mailed December 2, 2005, claims 5, 8-14 and 15 were rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. It is respectfully submitted that the amendment to claim 15 renders the Section 112 rejection to claim 15 moot.

The term "high energy" in claim 5 has been objected to as being unclear in it's meaning in the claims and is not defined in specification. Although the term "high energy" has been deleted from the claim and the objection is moot, nevertheless it may be placed on record that applicants do not agree with the objection as explained hereafter. This is because the term as used would ordinarily be understood by a person of skill in the art. A person of skill in the art would understand the term "high energy" crystalline form as a crystal form or polymorph having higher free energy than the most stable form of metaxalone under conditions of ambient temperature and pressure. The following reference "Polymorphism in Pharmaceutical Solids", Brittain H. G., Marcel Dekker Inc., 1999 in pages 10 to 18 and page 290 (enclosed with the Supplemental IDS concurrently filed herewith) makes it amply clear. For example, page 14 of this reference states:

Each polymorph yields an energy diagram similar to Figure 6 although the values of G, H and the slopes of the curves at a given temperature are expected to differ between different polymorphs.

Because each polymorph has its own distinctive crystal lattice, it has it's own distinctive Morse potential energy curve for the dependence of the intermolecular interaction energies with intermolecular distance. . . . Figure 9 presents a series of Morse curves, one for each polymorph (A, B and C) and for the liquid state of a typical substance of pharmaceutical interest.

Further pages 17-18 of this reference states: "Hence, because the most stable polymorph under defined conditions of temperature and pressure has the lowest Gibb's Free energy it also has the lowest values of fugacity, vapor pressure, thermodynamic activity, and solubility in any given solvent" Further, page 18 summarizes that "[T]he most stable polymorph has the lowest Gibb's free energy, fugacity, vapor pressure, thermodynamic activity, solubility and dissolution rate per unit surface area in any solvent, and rate of reaction, including decomposition rate." Page 290 states "Any metastable phase will have a higher free energy than would a thermodynamically stable phase, and it will undergo a phase transformation to the more stable phase once the activation energy barrier is overcome."

Further description from a widely used reference used in undergraduate programs towards a pharmacy degree would make it amply clear that the person of skill in the art would understand the meaning of the term "high energy crystalline form." See e.g., the reference entitled "The Theory and Practice of Industrial Pharmacy", Lachman L. et al., Lea & Febiger Varghese, third edition, Indian edition, 1987, page 222 (enclosed with the Supplemental IDS concurrently filed herewith). It states that "For example, polymorphs with weak attractive forces (thus, in a high energy state) exhibit greater solubility than those with strong attractive forces."

Claims 8-14 were also rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully traverse this rejection. The term "undersize" is well known to a person of ordinary skill in the art and does not need to be elaborated further. See "Physical Pharmacy", 4th edition, Martin A.N., Waverly International, Maryland, 1993, Indian reprint 1994, page nos. 426-429 enclosed with the Supplemental IDS

filed concurrently herewith and hereinafter referred to as the Martin reference. See cumulative % frequency undersize plot (Table 16-4 and Fig 16-3, of the Martin reference). On page 427, the Martin reference states “An alternative method of representing the data is to plot either the cumulative percent over or under a particular size versus particle size.” On page 429 in Figure 16-3 such a plot is illustrated. On page 428 the abbreviated form “% undersize or % oversize” in place of the full term “cumulative percent frequency undersize or oversize”, respectively has been used. Thus, the term “cumulative percent frequency undersize or oversize” is well known and understood by a person of ordinary skill in the art who also knows that the terms may be abbreviated to percent undersize or oversize.

The Examiner’s objection about Claims 8 and 12-14 being indefinite, broad range together with a narrow range, is noted. Applicants believe that the cumulative percent frequency data limitations are not viewed in this manner and the limitations are not narrow ranges within a broad range. For example, these three limitations are merely 3 points on a cumulative percent frequency curve such as for example curves illustrated in Figures 16-3 or Figure 16-5 on page 429 of the Martin reference. By defining the three points the whole curve is represented. However, the applicants have amended claim 8 to recite only a single point and the rejection of claim 8 is now moot. In view of the above discussion, applicants respectfully submit that amended claims 12-14 are in condition for allowance.

Claim 1-2 and 15 were rejected under 35 U.S.C. 102(e) as being anticipated by Scaife et al. U.S. Patent No. 6,407,128. Claims 1-15 were rejected under 35 U.S.C. 103 as being unpatentable over Scaife et al. in view of Gilis et al. U.S. Patent No. 6,030,988. Claims 16-18 were rejected under 35 U.S.C. 103 as being unpatentable over Scaife et al. as applied to claims 1-

15 above in view of Cheng et al. U.S. Patent No. 6,099,859. Claims 23-24 were rejected under 35 U.S.C. 103 as being unpatentable over Scaife et al. as applied to claims 1-15 above.

The Scaife patent investigates the effect of food on metaxalone absorption to evaluate the bioavailability, when given with or without food (see column 2, lines 51-60) and teaches that metaxalone bioavailability can be increased when it is administered to the patients with food (see column 2, lines 5-36). In Scaife it is not the composition that has enhanced bioavailability in itself, but it needs to be administered along with the food to make it bioavailable to maximize the therapeutic effect (column 2, lines 37-42). It is the combination with food or the effects of food that cause the enhanced bioavailability as opposed to the instant invention where the composition itself has an enhanced bioavailability and there is no requirement that the patient need or need not have food when the composition is administered to the patient.

Claim 1 of the present invention has been amended to now claim a “pharmaceutical composition comprising metaxalone and at least one pharmaceutically acceptable excipient[s], characterized in that the pharmaceutical composition has enhanced oral bioavailability as compared to a composition having a conventional pharmaceutical composition of metaxalone available commercially when administered without food to a patient who has fasted.

The amendment to claim 1 is supported by description of the present invention. See page 2, paragraph 3 (pharmaceutical composition having “enhanced bioavailability”) in conjunction with the following paragraph 4 (bioavailability of the disclosed composition of the present invention is “independent of whether the composition is administered to the patient with food or on an empty stomach”). Similarly last paragraph on page 5 extending to page 6 recites both these features of the instant invention. Example 2, which shows the enhanced bioavailability of

the present invention over a conventional pharmaceutical composition of metaxalone available commercially when administered without food to patients who have fasted, further supports the amendment to claim 1.

Scaife et al. specifically teach the administration of their metaxalone particles with food for increased oral bioavailability. Thus amended claim 1 is distinguished over Scaife et al. Further claim 2 is distinguished from Scaife et al. because Scaife et al. do not teach metaxalone in a pharmaceutically acceptable solubility-improved form.

The applicants would like to point out that, the reference on which the examiner has relied for 102(e) objection, namely the Scaife et al. patent is listed for the commercially available metaxalone composition Skelaxin® in the Orange Book and the applicants have provided comparative data in Example 2 to show that the metaxalone composition of the present invention has enhanced bioavailability as compared to commercially available metaxalone composition when administered to patient on an empty stomach.

The specification of the present application provides a side-by-side comparison testing between the present invention and Skelaxin®. *See* Tables 6-8 of the specification of the present application for the side-by-side comparison test results. The Skelaxin® used in this side-by-side comparison testing is the composition disclosed in Scaife et al. U.S. Patent No. 6,407,128, which is the patent listed in the Orange Book for Skelaxin® (corresponding to New Drug Application No. 13-217). *See* <http://www.fda.gov/cder/orange/obannual.pdf>, “Approved Drug Products,” at pp. 3-241, 6-167, A-48, B-59, and ADA 78 of 136 (enclosed with the Supplemental IDS concurrently filed herewith). Accord,

<http://www.fda.gov/cder/foi/label/2002/13217s036lbl.pdf> (which shows that Skelaxin® corresponds to New Drug Application No. 13-217), and <http://www.fda.gov/cder/ob/> , “Electronic Orange Book” (site where searching can be done by “Proprietary Name” or by “Patent”) – search done for the “Proprietary Name” Skelaxin®, shows that Skelaxin® corresponds to New Drug Application No. 13-217, and search done for Patent 6,407,128 shows that Patent 6,407,128 corresponds to the product identified in New Drug Application No. 13-217. See enclosures to Supplemental IDS filed concurrently herewith.

Example 1 and Tables 2-4 of the present application teach the preparation of a pharmaceutical composition of the present invention. Example 2 and Tables 6-8 of the present application show that the present invention provides unexpected results of enhanced bioavailability on an empty stomach over the composition disclosed in Scaife et al.

The secondary reference, Gilis et al. does not teach a pharmaceutical composition comprising metaxalone. Gilis et al. teaches a pharmaceutical composition comprising a certain racemic form of cisapride for the treatment of a gastrointestinal disorder without a drug food interaction. Gilis et al. in no way suggests that the use of certain sized particles of metaxalone in a pharmaceutical composition as claimed in the present invention would lead to the unexpected result of increased oral bioavailability of metaxalone independent of whether the composition is administered to a patient with food or without food.

The unexpected results are not taught or suggested by Gilis et al., which teaches a wholly different composition for treating a wholly different condition. The fact that Scaife et al. cites to Gilis et al. yet fails to disclose the present claimed invention is strong evidence that one of ordinary skill in the art would not have been motivated to combine Scaife et al. and Gilis et al. to

provide the present invention. One of ordinary skill in the art would not be motivated to go in an opposite direction of Scaife et al., *i.e.*, which teaches administration of metaxalone with food, and achieve enhanced bioavailability independent of whether the composition is administered to a patient with food or without food.

Cheng et al. does not teach a pharmaceutical composition comprising metaxalone. Cheng et al. relates to controlled release tablet having a core containing an antihyperglycemic drug and a semipermeable membrane coating the core and at least one passageway in the membrane for the release of the drug. Cheng et al.'s compositions are of antihyperglycemic drugs like metformin or buformin for treatment of diabetes mellitus (see column 3, lines 34-39). Among many other excipients that can be used as absorption enhancers, Cheng et al. refers to sodium lauryl sulfate. The fact that Scaife et al. cites to Cheng et al. yet fails to disclose the present claimed invention is strong evidence that one of ordinary skill in the art would not have been motivated to combine Scaife et al. and Cheng et al. to provide the invention claimed in claims 16-18 of the present invention. One of ordinary skill in the art would not be motivated to go in an opposite direction of Scaife et al., *i.e.*, which teaches administration of metaxalone with food, and achieve enhanced bioavailability independent of whether the composition is administered to a patient with food or without food.

Scaife et al. does not teach/suggest each and every feature recited in the amended claim 1 or claim 2. Scaife et al. does not teach/suggest a pharmaceutical composition of metaxalone in combination with a non-steroidal anti-inflammatory drug. Claims 23 and 24, which are dependent on claim 1 and 2, respectively are not obvious in view of Scaife et al.

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Because Scaife et al. and Gilis et al., or Scaife et al. and Cheng et al. singly or combined, do not teach or suggest each and every feature recited in the amended claims, the claimed invention is novel and non-obvious in view of the prior art. Accordingly, applicants respectfully request that the prior art rejections be withdrawn.

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,
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